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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/910,087	07/20/2001	Peter Anthony Koopman	10981AZ	2931

7590 07/16/2003  
Scully, Scott, Murphy & Presser  
400 Garden City Plaza  
Garden City, NY 11530

EXAMINER

NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 07/16/2003

9

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.  
**09/910,087**

Applicant(s)  
**Koopman**

Examiner  
**Dave Nguyen**

Art Unit  
**1632**



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on May 12, 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 7-15, 17, and 18 is/are pending in the application.
- 4a) Of the above, claim(s) 7, 9-13, 17, and 18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 8, 14, and 15 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some\* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_ 6) ☐ Other: \_\_\_\_\_

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Claims 8, 14, 15 have been canceled, claim 16 has been canceled by the amendment dated May 2, 2003. Claims 7, 9-13, 17-18 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention. A complete response to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) MPEP 821.01.

Claims 8, 14-15 are pending for examination.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8 and 14-15 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for

A method of increasing cartilage deposition in a mammal suffering from Sox-9 deficiency that leads to a breakage, degeneration, depletion or damage of bone or cartilage forming cells in said mammal, the method comprising administering directly to said cells a DNA molecule comprising a promoter operably linked to the nucleotide sequence as set forth in SEQ ID NO: 20, or a nucleotide sequence coding for a SOC-9 polypeptide wherein said SOC-9 polypeptide comprises the amino acid sequence as set forth in SEQ DI NO: 21,

does not reasonably provide enablement for any other claimed embodiment as embraced by the presently pending claimed invention. The specification does not enable any person skilled in the art

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to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The application reviewed the state of the prior art regarding known SOX genes and their biological functions as transcription factors which play a biological role during a development process (pages 2-5).

With respect to the biological activity of the human Sox-9 gene or its encoded protein product, the application teaches that SEQ ID NO: 20 plays an important role in development (page 5), and that experimental bone fracture induces expression of the SOX-9 polypeptide (SEQ ID NO: 19). However, the claimed invention embraces a gene therapy treatment in any animal (including reptiles, birds, amphibians, mammals) any disease associated with a breakage, degeneration, depletion or damage of bone or cartilage, wherein the disease is not necessarily caused by SOX-9 deficiency or its loss of function. While the as-filed specification coupled with the art of record including those submitted in the latest response provides a reasonable enablement for

A method of increasing cartilage deposition in a mammal suffering from Sox-9 deficiency that leads to a breakage, degeneration, depletion or damage of bone or cartilage forming cells in said mammal, the method comprising administering directly to said cells a DNA molecule comprising a promoter operably linked to the nucleotide sequence as set forth in SEQ ID NO: 20, or a nucleotide sequence coding for a SOC-9 polypeptide wherein said SOC-9 polypeptide comprises the amino acid sequence as set forth in SEQ DI NO: 21,

neither the application nor the incorporated references demonstrate any therapeutic effect in any other animal having a bone or cartilage disease. Neither the application nor the claims recite which subjects and which bone diseases or disorders are affected by the claimed treatments, the target sites, the effective dosage for accomplishing a therapeutic effect *in vivo*, the administration routes, and the stated effect of the claimed methods which are essential for the success of the claimed treatments. In

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addition to breadth of the claims that embrace non-mammalian subjects and any cartilage or bone associated disease or disorder which is not related to SOX-9 deficiency, the claimed invention also embrace any gene therapy protocol and/or any route of administration of any DNA regardless of the presence of an operably linked promoter or expression cassette, More specifically as to gene therapy methods as claimed for regeneration of bone and cartilage in all animals including humans, amphibians, reptiles, and fish, the application and the art of record provide no *in vivo* and/or *in vitro* examples to demonstrate the biological activity of any DNA sequence as claimed for regeneration of bone or cartilage any animal other than rats and mice. Major considerations for any gene transfer or gene therapy protocol involve issues such as amount of DNA constructs to be administered, what amount is considered to be therapeutically effective for all of the claimed nucleic acid molecules, the route and time course of administration, the sites of administration, successful uptake of the claimed DNA at the target site, expression of the DNA at the target site in amounts of effecting the claimed methods (Verma *et al.*, Nature, Vol. 389, pp. 239-242, 1997). None of these considerations are adequately addressed in the specification to enable others to practice the invention without the exercise of undue experimentation. Verma *et al.* specifically teach that problems including the lack of efficient delivery systems, lack of sustained expression remain formidable challenges (page 239, column 1). Gunzburg *et al.* (Molecular Medicine Today, pp. 410-417, 1995) state that "clearly, there are many problems to be overcome before gene therapy becomes a widely used treatment, and it will probably only ever complement rather than replace existing therapies" (p. 417). Gunzburg *et al.* also state that "the efficiency of gene delivery is perhaps the most limiting technical problem; this will require extensive modifications to existing vector systems or even the construction and development of new gene delivery systems (p. 416, column 2, last paragraph). Neither the specification nor the incorporated references provide sufficient guidance as to the appropriate dosage for each bone/cartilage disease to be treated or routes of administration or other important parameters of therapy in regard he regeneration of bone or

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cartilage at any target site in any animals. The state of the targeted gene therapy art remains unpredictable even in 1999. Meng *et al.* (Gene Therapy of Cancer, Chapter I, pp. 3-20, 1999) teach that factors including specific genes used for a treatment, gene delivery vectors, routes of administration, and gene expression are all critical for the success of a gene therapy method (pages 4-6). For example, Meng *et al.* teach that "it is difficult to prepare sufficiently high titers of retroviruses for *in vivo* gene therapy", that "the most significant drawback to adenoviruses, however, is that they elicit a strong host immune response", and that "although it may seem intuitive that a heightened immune response may be good in cancer gene therapy, it is less desirable on a practical scale because the immune response helps to eliminate the vector and to decrease the expression of the transduced gene" (p. 4, column 2, last paragraph). Meng *et al.* further teach that "although animal studies have suggested low toxicity and excellent efficacy, these investigations have been limited by the use of immuno-deficient mice" (p. 6, column 1).

With respect to administration routes, Meng *et al.* teach that delivery of virally expressed genes by intravascular or intracavitary injections also presents barriers to the delivery of the target genes (p. 6, column 1). For example, Meng *et al.* state:

In intravascular administration, instillation into a peripheral vein dilutes the vehicle, so only a small portion may ultimately reach the tumor. Intravascular administration also elicits a powerful immune response. Tropism for organs such as the liver, for example by adenovirus, can be a disadvantage if delivery is intended elsewhere or may be advantageous if the liver is the target. Even with regional intravascular administration, the virus must traverse the endothelial wall and travel against pressures within an expanding tumor mass. In the case of intracavitary administration (i.e., intrapleural or intraperitoneal), the surface of the tumor mass is coated by virus, but intratumoral delivery within a solid mass represents an important barrier (page 6, column 1).

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The specification fails to provide sufficient guidance and/or evidence to address all of the major issues as to the unpredictability of nature of the art, and of gene therapy at the time the invention was made. Thus, when weighing the guidance from the disclosure and all of the evidences as a whole, especially the unpredictability of the activities Sox-9 encoded DNA sequences in the treatment of regenerating bones or cartilage in any animal wherein the disease is not caused by SOX-9 inactivation or deficiency, the lack of reasonable correlation between a simple direct administration of a replication defective adenovirus vectors to cartilage forming cells in the intervertebral disc of rats (provided by the post-filing art submitted May 12, 2003) and a therapeutic treatment of any other cartilage or bone associated disorder in any animal wherein any route of administration is embrace, a reasonable unpredictability of gene therapy and/or targeted gene therapy, it is apparent that one skilled in the art would not be able to practice the full breadth of the claimed invention, without undue experimentation, at the time the invention was made, particularly on the basis of applicant's disclosure and the doubts expressed in the art of record. Note that it is known in the art that while some progress has been made toward human gene therapy, only a handful of clinical trials and very limited anecdotal results has been reported to date. Thus, the unpredictability of a particular art area alone provides reasonable doubt as to the accuracy of the broad statement made in support of enablement of a claim.

Applicant's response (dated May 2, 2003) has been considered by the examiner and is found partially persuasive for the reasons set forth in the above stated rejection. However, the scope rejection is properly maintained, particularly in view of the reasons set forth above. Likewise, all of the exhibits 1-6 have been considered but are not sufficient in overcoming the scope rejection as stated above. Applicant asserts on page 6 that ex vivo implantation or gene therapy methodology is embraced by the claimed invention, however, the claimed invention clearly set forth that "a nucleic acid" administered to an animal, and as such, the examiner would like to clarify that this particular limitation taught from the specification can not be read into the presently pending claims as written presently. An administered

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DNA is not the same as genetically engineered cells expressing a SOX-9 protein. The claimed invention is drawn to an *in vivo* gene therapy only and as such, and to the extent that the as-filed specification and the claims embrace any use of any DNA (naked DNA, viral DNA) for any administration route to any target cells in any animal as claimed, the guidance provided by the specification is not sufficient to overcome the issues as set forth in the above stated rejection.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051**.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Trong Nguyen  
Primary Examiner  
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DAVE T. NGUYEN  
PRIMARY EXAMINER